

Targeting sonic hedgehog-associated medulloblastoma through inhibition of Aurora and Polo-like kinases.

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Public Summary:

Medulloblastoma is the most common malignant brain tumor in children. Although aggressive surgery, radiation, and chemotherapy have improved outcomes, survivors suffer severe long-term side effects, and many patients still succumb to their disease. For patients whose tumors are driven by mutations in the sonic hedgehog (SHH) pathway, SHH antagonists offer some hope. However, many SHH-associated medulloblastomas do not respond to these drugs, and those that do may develop resistance. Therefore, more effective treatment strategies are needed for both SHH and non-SHH-associated medulloblastoma. One such strategy involves targeting the cells that are critical for maintaining tumor growth, known as tumor-propagating cells (TPC). We previously identified a population of TPCs in tumors from patched mutant mice, a model for SHH-dependent medulloblastoma. These cells express the surface antigen CD15/SSEA-1 and have elevated levels of genes associated with the G2-M phases of the cell cycle. Here, we show that CD15(+) cells progress more rapidly through the cell cycle than CD15(-) cells and contain an increased proportion of cells in G2-M, suggesting that they might be vulnerable to inhibitors of this phase. Indeed, exposure of tumor cells to inhibitors of Aurora kinase (Aurk) and Polo-like kinases (Plk), key regulators of G2-M, induces cell-cycle arrest, apoptosis, and enhanced sensitivity to conventional chemotherapy. Moreover, treatment of tumor-bearing mice with these agents significantly inhibits tumor progression. Importantly, cells from human patient-derived medulloblastoma xenografts are also sensitive to Aurk and Plk inhibitors. Our findings suggest that targeting G2-M regulators may represent a novel approach for treatment of human medulloblastoma.

Scientific Abstract:

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